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TITLE: Characterization of Breast Masses Using a New Method  
of Ultrasound Contrast Agent Imaging in 3D Mapping  
of Vascular Anomalies

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<b>13. ABSTRACT (Maximum 200 Words)</b>  Doppler ultrasound and other imaging modalities have been used to assess characteristics of vasculature associated with malignant breast masses. Specific to our institution, promising results have been achieved in discriminating benign from malignant masses using Doppler vascularity measures in conjunction with ultrasound grayscale features.  The purpose of this work is to develop an innovative dual-transducer method to control the destruction and imaging of ultrasound contrast during 3D ultrasound scanning of suspicious breast masses. This method, which involves sequential scanning and co-registration of image volumes acquired during contrast refill, should provide mapping of vascularity around these masses and highlight the associated anatomic variation in mean transit time.  In the coming year, this new imaging scheme will be evaluated in a small patient population to begin to establish the refill characteristics for a variety of suspicious breast masses, and appropriate mathematical models will be developed to characterize contrast agent refilling following destruction specific to the dual-transducer system. Experimental assessment of contrast agent life-span, destruction characteristics, and refill imaging has been undertaken in flow phantoms. A software system will be developed to visualize quantification of regional perfusion in and around the region of interest. Year one results are presented here.				
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## Introduction

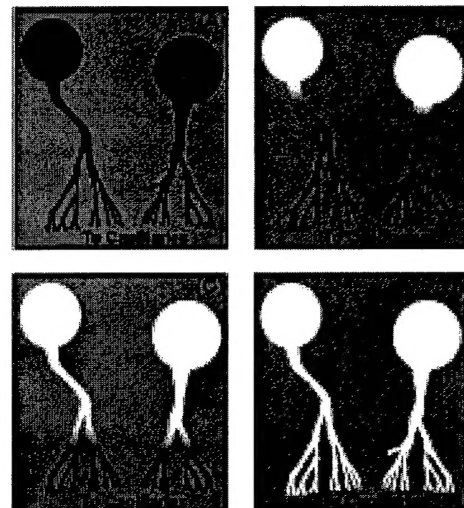
The overall purpose of this work is to develop an innovative dual-transducer based 3D ultrasound contrast imaging system for characterizing suspicious breast masses. The proposed method will provide a mapping of vascularity around such masses and a measure related to local variations in mean blood transit time. It is expected that the time improvement over other suggested methods of such 3D mapping should be at least an order of magnitude. It is hypothesized that these measures, now feasible, will serve to increase our understanding of tumor biology in terms of vessel formation. The new system should also enhance our ability to discriminate benign from malignant lesions with a method more definitive than currently available. The scope of year one includes some logical rearrangement of tasks from the original proposal. For example, the proposed schedule incorporated complete design, construction, and testing of our mechanical imaging system and somewhat extensive modelling of contrast agent destruction. Instead, it became obvious that we needed to shift flow-phantom tasks (originally slated for months 13-24) into year 1. While accomplishing experimental tasks from year 2, we were still able to develop the mechanical prototype (and its precursor), model some of the flow characteristics, and measure ultrasound beam profiles. More extensive modelling will be performed in the current year, and we expect that the patient studies will be shifted about 6 months.

## Body

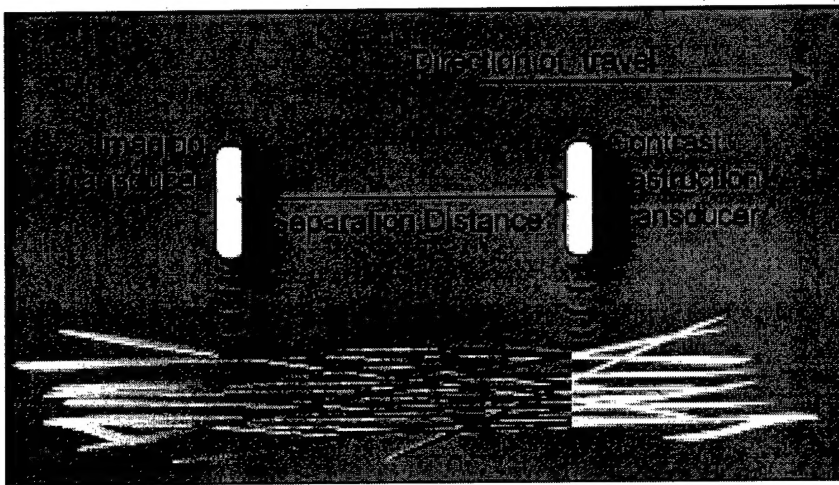
### Background:

As mentioned in the original proposal, previous studies by other investigators have demonstrated characteristics of vasculature associated with malignant breast masses. These have included thin-walled blood vessels, increased microvessel density, disordered neo-vascularization penetrating the mass, arteriovenous shunting, and a variety of characteristic Doppler ultrasound and histologic findings [Lee et al. 1996, Peters-Engl et al. 1998]. Some studies strongly suggest that flow velocity demonstrates significant correlation with tumor size [Peters-Engl et al. 1998] and that parameters such as vessel count and flow velocity display significant differences between malignant and benign lesions [Madjar et al. 1994]. A shortcoming of most of these trials has been the limitation of 2D images in assessing overall vascular morphology, density, and velocity distributions.

Given the limitation of 2D studies and the relative sparseness of breast vasculature, our group has investigated the utility of 3D breast imaging for several years. Recently published results [LeCarpentier et al. 1999] indicate that one of our Doppler vascularity measures, Speed Weighted pixel Density (SWD), is statistically different for benign versus malignant lesions and comparable to ultrasound grayscale (GS) evaluation. More recent work in a 38 patient pool suggests that multi-variable indices (which include both SWD and GS features) demonstrate good results in differentiating



**Figure1.** Schematic representation of ultrasound contrast refill. An ultrasound beam is used to destroy contrast agent in all vessels in the imaging plane (A). The larger vessels quickly refill (B) and feed the smaller arteries and arterioles with fresh contrast (C & D). Over time, capillary refill can be visualized.



**Figure 2.** Schematic of dual-transducer method for monitoring capillary refill. The high intensity transducer is used to destroy contrast and create a zero-contrast-enhanced wavefront. The low intensity imaging transducer follows behind at some fixed time (distance). By sequentially scanning the same region using different delays, a refill-time map can be constructed for the volume.

benign from malignant breast masses well beyond GS evaluation alone [Bhatti et al. 2000]. In a follow-up study (submitted and accepted for publication), the results of the initial 38 patients (18 benign, 20 malignant) were used to form a learning set (A), and multivariable indices were established using bayesian discriminators. In Group A, 94% specificity was achieved for the SWD-Age-GS index at 100% sensitivity. Applying the same linear function to the second pool

(B) resulted in 86% specificity at sensitivity of 100% [LeCarpentier et al. 2002]. The diagnostic performance of SWD in our second patient population strongly suggests the utility of vascular indices in the characterization of breast masses.

In addition to Doppler imaging, a number of investigators have performed extensive evaluation of ultrasound contrast agents in the evaluation of blood flow. Success of low-frame-rate imaging (termed "transient response imaging" or "interval imaging") is related to the "refill" of agent into tissue [Porter and Xie 1995, Porter et al. 1997]. Monitoring refilling has estimated the perfusion in tissue [Wei et al. 1998] and specific pulsing sequences such as "Flash Echo Imaging" (Toshiba Medical Systems) and "Power Pulse Inversion" (ATL/Phillips) have been developed on ultrasound scanners to obtain refill information. Studies at our institution [Fowlkes et al. 1998] have shown that it is possible to destroy contrast agent flow in arteries to produce interruptions with signal separation up to 30 dB. Similar interruptions allow downstream contrast agent to clear and the release of a short bolus by temporarily turning off the field [Rhee et al. 1998]. All of these methods rely on controlled destruction of contrast agents and subsequent reflow into tissue. Complications associated with such measurements in 3D are addressed in this work.

Figure 1 shows a general schematic of contrast disruption and refill. An ultrasound beam is used to destroy contrast agent in all vessels in the imaging plane. The larger vessels with significant volume flow and high flow rates would quickly refill. The volumes of interest, however, are slower flow in the capillary bed. As the arterioles are filled, the contrast can be visualized, and eventually capillary refill will be seen. Figure 2 depicts the dual-transducer imaging scheme. For the sake of discussion, consider the case of a patient under constant drip infusion of ultrasound contrast agent. At steady state, the imaged blood is 100% contrast enhanced. By translating an ultrasound transducer transmitting a sequence of high-intensity pulses, a wavefront of maximally broken contrast or "zero-contrast-enhanced" tissue is formed. Although the figure shows vessels virtually flowing in the same direction for simplicity, a model will be developed to describe the more "real-world" scenario of isotropically distributed flow into and out of the particular volume of interest. The second transducer, which arrives at the same location at time 2, images the partially refilled volume. After modeling of this scenario is completed at a future time, the expected flow-back distribution for a given image slab will be used to

interpret this subsequent image. This process can be repeated multiple times using different delay settings between contrast destruction and imaging to estimate refill rates for every region in the overall imaged volume.

#### Specific Tasks:

In the originally proposal document, the approved statement of work included the five major tasks listed below:

Task 1 (months 1-6): Model input function of contrast agent destruction:

- (a) Generate mathematical flow model
- (b) Measure beam profile
- (c) Incorporate various profiles, flow, and scan rates

Task 2 (months 3-12): Assemble and test mechanical imaging scan system:

- (a) Design and construct mechanical translation system
- (b) Design and test electrical interface
- (c) Design and test interface software

Task 3 (months 13-24): Design and perform experimental assessment of imaging system design:

- (a) Evaluate performance on strict flow tube models
- (b) Evaluate performance on kidney phantom
- (c) Evaluate 3 point method of refill curve modelling

Task 4 (months 1-24): Develop and assess visualization and quantification software:

- (a) Verify flow model
- (b) Develop regional mapping software (\*can start as soon as the project begins)
- (c) Develop and evaluate parametric histogram visualization scheme

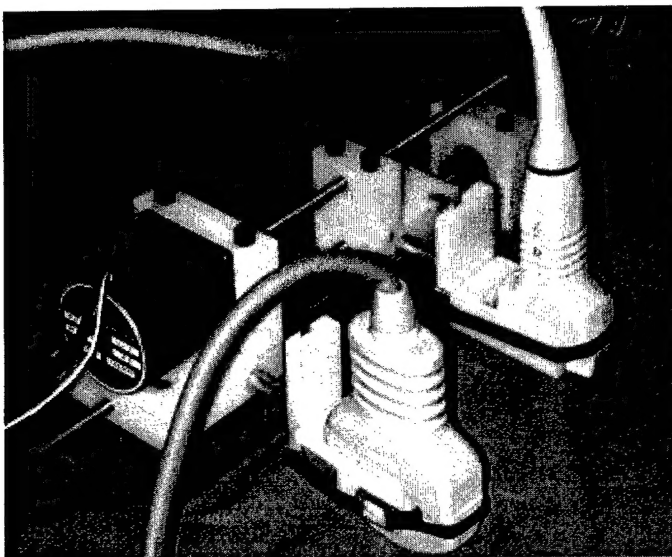
Task 5 (months 13-36): Assess system and 3D imaging software on small patient population:

- (a) Recruit patients
- (b) Perform scans
- (c) Evaluate refill maps and parameterize
- (d) Test discriminators

Task 6 (months 30-36): Overall data analysis and write-up

In this first year, some of the priorities have been rearranged while remaining within the overall approved statement of work. For example, the proposed schedule incorporated complete design, construction, and testing of our mechanical imaging system and somewhat extensive modelling of contrast agent destruction. Instead, it became obvious that we needed to shift flow-phantom tasks (originally slated for months 13-24) into year 1. While accomplishing experimental tasks from year 2, we were still able to develop the mechanical prototype (and its precursor), model some of the flow characteristics, and measure ultrasound beam profiles. More extensive modelling will be performed in the current year, and we expect that the patient studies will be shifted about 6 months, into the third quarter of year 2.

In terms of specifics originally proposed for year 1, ultrasound beam profiles were measured to the extent that the focal points of various transducers were established. This information was eventually used in flow experiments to optimally position the center of the tube in tube-flow phantoms.



**Figure 3.** DualTransducer Scanning Apparatus. The scanning apparatus is in prototype condition at present. Two stepper motors (3.5 and 1.2 Amps) control the contrast destruction transducer from the Toshiba PowerVision 8000 and the imaging transducer attached to the GE Logiq 9.

Preliminary modelling was accomplished relevant to flow in explaining experimental image results.

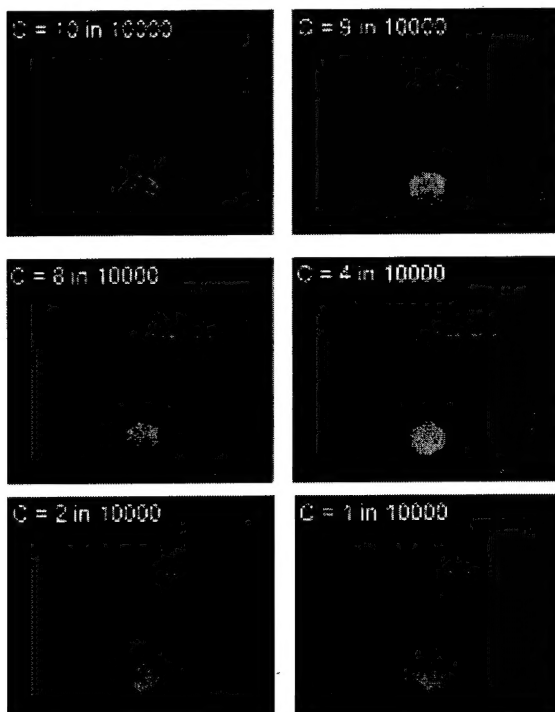
An electrical hardware and software interface was developed and tested for an early prototype of the imaging scan system.

Unfortunately, we were unable to obtain the required operating speed or torque necessary to translate the system fully loaded with the two transducers. The system was redesigned with larger motors, rated at 1.2 A and 3.5 A, able to control the separation distance and overall scanning translation, respectively.

It is shown in Figure 3. The electrical interface and software is still in the development stage.

The development of the regional mapping software has begun in that software tools have been and continue to be developed to analyze

the ultrasound images. Specific to this project, a new scheme of imaging contrast agent has been developed to compensate for the confounding effects of shadowing by the contrast agent during the destruction pulse sequence. This scheme is discussed in the next sub-section.

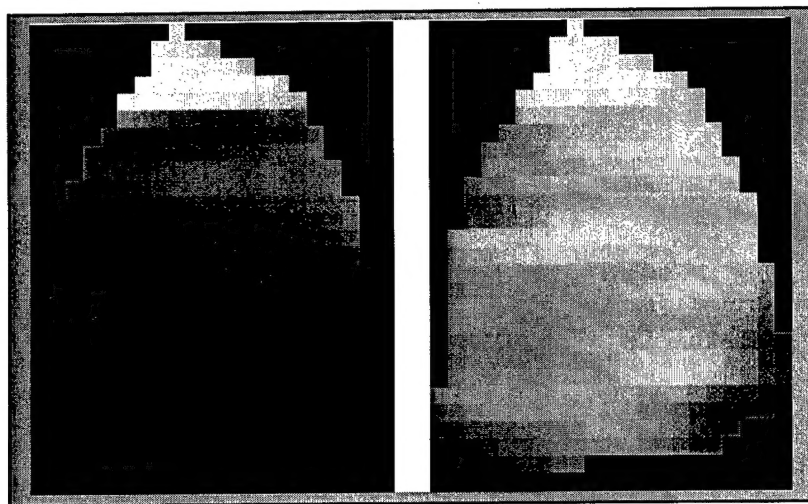


**Figure 4.** The effect of contrast agent concentration. These images (each averaged over 100 image planes) were acquired using a flow phantom, various concentrations (C) of Definity, and a Toshiba PowerVision 8000. Note how the agent "shadows" underlying flow at higher C, and its echogenicity is proportional to C at lower concentrations.

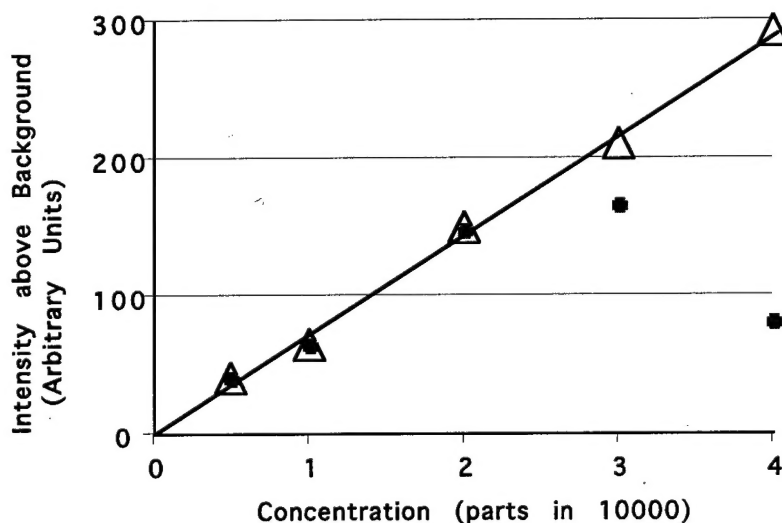
Besides the tasks specifically mentioned from the Year 1 work statement, a variety of studies have been performed using various flow models. These included the procurement and testing of a plasticized kidney phantom, which was unsuccessful, and the development of a variety of gel/tank phantoms which led to the agar gel phantom used in a number of contrast endurance tests, which demonstrated contrast life on the order of hours. Additional flow experiments (originally proposed for year 2) included the imaging of contrast as a function of concentration, and finally actual successful imaging and reconstruction of a 3D volume using the proposed technique. These results are presented in the following sub-section as well.

#### Results:

The contrast agent Definity was flowed (at various concentrations from 1:10000 to 10:10000) through a channel in an agar gel phantom, and imaged over time. For each concentration, 100 images were acquired and averaged. Figure 4 demonstrates the effects of increasing concentration of Definity. At concentrations above 4 in 10000, the effects of contrast agent shadowing become apparent. This essentially means that if one were to



**Figure 5.** Definity imaged at 4 parts in 10000. The grayscale map for these images was selected to highlight the effect of shadowing. A tube similar to that imaged in Figure 4 was used to acquire these images, which are segmented and magnified versions of the originals. Five contrast destruction sequences (of 15 pulses each) were performed with sufficient recovery time between each sequence to prevent sequence interaction. The images acquired for the sequences were averaged pulse by pulse (i.e. all pulse 1s, all pulse 2s, etc.) to produce an average pulse sequence. On the left is the image that results from subtracting the last image of the average pulse sequence from the first, as is generally done. Note the shadowing caused by the contrast at the upper part of the tube. Conversely, the image on the right was produced by generating a maximum projection image through the average pulse sequence. This technique allows contrast imaged during pulses after the first one to contribute to the resultant image. Note: All data manipulations were calculated using decompressed images which represent real intensity.



**Figure 6.** Contrast intensity versus concentration. The graph shows the effects of contrast concentration on imaging in a 6 mm tube (as in Figure 5). Five destruction sequences (i.e. 5 "runs") were performed for each test concentration (as described in Figure 5), and the runs were then averaged to give an average destruction sequence. The solid circles (●) represent the mean intensity of the tube obtained by subtracting the intensity after the 15 destruction pulses from that obtained with the first pulse. Note that at higher concentrations, the scheme fails as demonstrated by the intensity drop-off. This trend was even more exaggerated at higher concentrations. The larger open triangles represent the average intensity of the imaged tube using the maximum projection technique. Note the linear relationship between intensity and concentration.

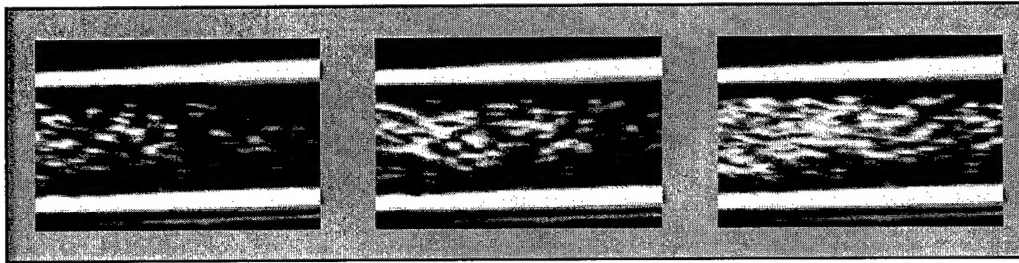
obtain mean intensity values from the region of interest (i.e. within the channel), high concentrations of contrast would correspond to mean intensities much lower than expected. In such cases, where shadowing plays a major role, the estimate of the amount of fluid (or blood in the real-world scenario) present based on the amount of signal would be low.

To address this issue, an imaging scheme was developed to account for these shadowing effects. In our typical imaging scenario, the contrast is imaged by first exposing the field to a sequence of ultrasound pulses, which effectively destroy the agent. Next, the first image in the pulse sequence is subtracted from the last image. Under conditions where all of the contrast present is visible (i.e. imaged) by the first pulse in the sequence, the resultant subtraction image represents a contrast-only image (or at least an image containing contrast plus baseline). At low concentrations, one would expect such a subtraction scheme to accurately reflect the real amount and distribution of contrast agent. At higher concentrations, however, the upper layer blocks the imaging pulse, as is manifest by the observed shadowing artifact. In a typical 15-pulse destruction sequence, then, the image produced by the first pulse will show contrast in the upper regions and shadow in the lower regions. In images produced by subsequent pulses, the upper-most contrast will have been destroyed, and contrast at deeper

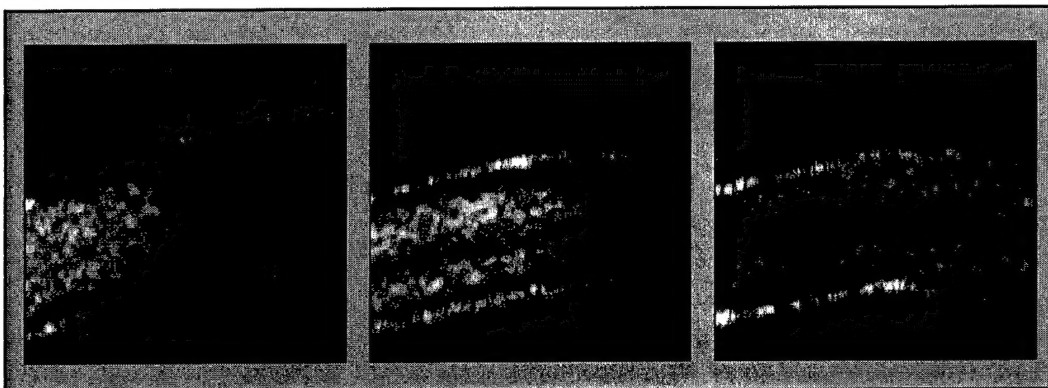
levels will result in a measurable signal (and perhaps still cause shadowing at even lower levels). The pulse sequence will proceed with increasing amounts of contrast agent destruction. The new scheme developed takes into account these dynamics. Instead of producing a first-minus-last subtraction image, it was hypothesized that more accurate results could be achieved by an image based on maximum intensity projection through the sequential images of the pulse sequence. In Figure 5, a comparison of the two methods is shown. The selected case shown demonstrates that the effect is present even in relatively moderate levels of contrast concentration (4 in 10000).

Figure 6 demonstrates the significance of the new imaging scheme over a broad range of contrast agent concentrations. One would typically expect the average signal level in a region of interest to be proportional to the concentration of scatters (i.e. contrast agent). The plot dramatically demonstrates that conventional subtraction images do not adequately relate concentration to image intensity. Conversely, there appears to be a strong linear relationship between contrast concentration and mean intensity when the image is created using the maximum projection method. Note also that the two schemes produce virtually identical results at lower concentrations.

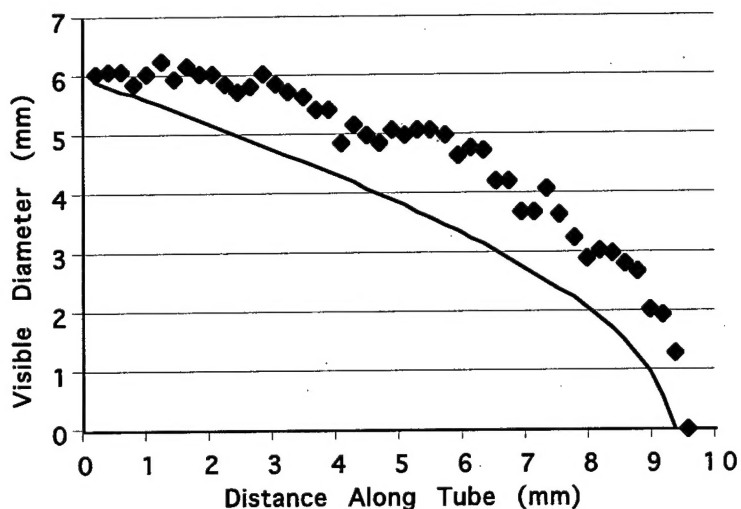
A laboratory set-up was developed to implement the dual-transducer method described in the introduction. In these cases, two transducers were fashioned to a linear motorized system which



**Figure 7.** Contrast agent flow imaged laterally in a flow-tube phantom. Contrast agent was infused into a tube phantom (6 mm diameter) at low concentrations to avoid shadowing and mimic clinical contrast agent infusion concentrations. Tube flow rates were comparable to large vessel flow rates ( $v > 1$  cm/s). The images above were taken with a GE Logic 9 in a low MI harmonic contrast imaging mode. The long axis of the transducer was placed along the axis of the tube (and flow). The evolution of the flow profile can be seen, although it is worth noting that any three-dimensional information is lost. The image volumes acquired to display the slower flow profiles shown in Figure 8 do not suffer from this limitation.

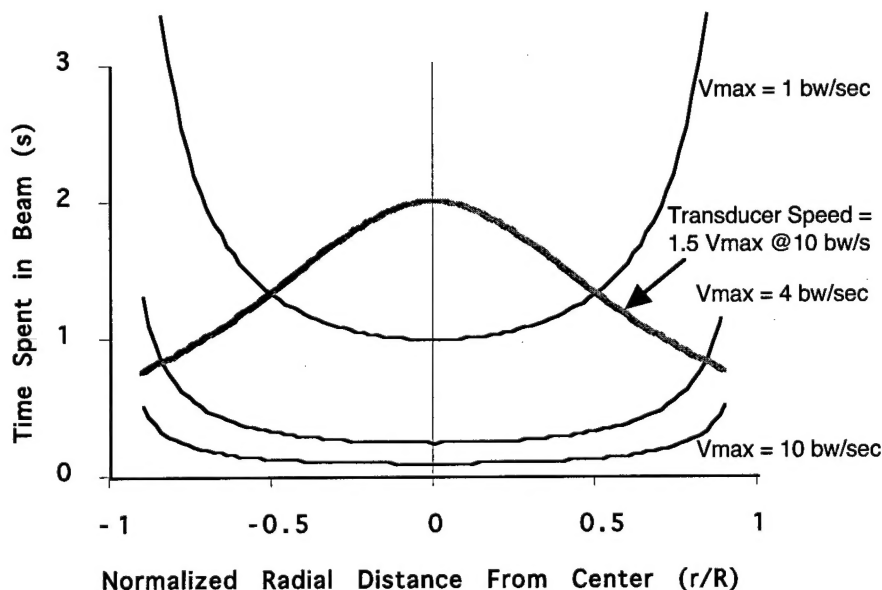


**Figure 8.** Reconstructed flow profiles using the dual-transducer technique. The Toshiba PowerVision 8000 was used as the "destructive" transducer while a GE Logiq 9 imaged refill at various times in a flow phantom. Again, a biologically relevant level of agent was used ( $C = 1$  in 10000). These reconstructed sequential images were acquired by adjusting the distance between the transducers as described in Figure 2 and the text. Each reconstruction displays a single "slice" reconstructed through the center of the entire image volume. The slices at the far left and middle were acquired 11 and 13 seconds after contrast destruction, respectively. Note the evolution of the flow profile. The image slice at the far right represents "steady state" at 24 seconds.



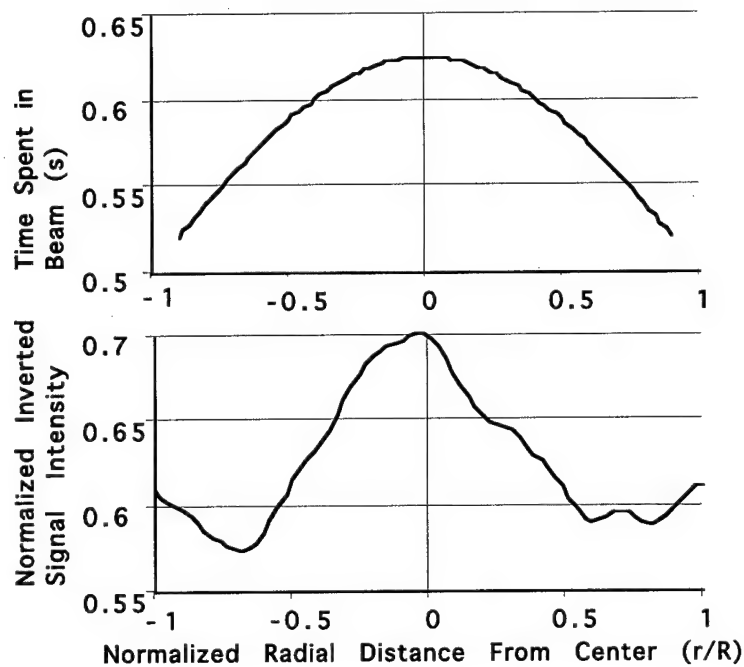
**Figure 9.** Observed parabolic flow profile obtained using the dual-transducer system. The solid line represents the theoretical diameter at the time (and distance) corresponding to time/distance of the images acquired with the GE Logic 9. The same images were used to reconstruct the longitudinal image in Figure 8. The offset between theoretical and observed diameters may be due to our inability at the time to precisely determine the slice corresponding to  $d=0$ . The (currently in development) software controller/feedback interface to the positioning system should alleviate errors so induced.

translated the transducer pair at a constant rate. The distance between the two transducers was varied, and destructive/imaging sequences were performed over a 6 mm flow tube. Prior to this, the same tube was imaged longitudinally during contrast agent influx. The results are shown in Figures 7 and 8. In both cases, the expected parabolic flow profile can be seen. In fact, the theoretical width of visible contrast agent was calculated and compared to the observed behavior shown in the far left image of Figure 8. These data are presented in Figure 9. One can also see an experimental artifact in the far right image of Figure 8. Note that the contrast appears to be depleted in the center of the tube. This may be due to the experimental set-up itself. In this



**Figure 10.** Simplified model of time spent in the ultrasound beam. Flow speeds are represented in units of "beam-widths" per second for normalization. Flow velocity ( $V$ ) as a function of radial distance ( $r$ ) from the center is considered parabolic [ $V(r) = V_{max} \cdot (1 - (r/R)^2)$  where  $V_{max}$  is the peak velocity and  $R$  is the tube radius]. With a stationary transducer, the fluid closest to the tube wall is exposed to the beam for the longest period of time, and these exposure durations decrease with increased flow velocity as shown by the three curves representing  $V_{max}$  at 1 bw/sec, 4 bw/sec, and 10 bw/sec. The thicker shaded curve represents what happens as the transducer is translated along the axis of the tube at a speed higher than the maximum flow velocity. In this case, where  $V_{max}$  was set to 10 bw/sec and the transducer speed was set to 1.5 times  $V_{max}$ , the maximum exposure to the beam occurs at the center of the tube. This may help explain the dark center region of the steady state image in Figure 8. That is, the contrast may be exposed to sufficient pulses in the center to break the bubbles and hence create a central zone where a low concentration of scatterers exists. The measured average intensity in the tube is compared to the exposure times in Figure 11.

case, both the destructive and imaging transducers traveled along the axis of the tube. For a stationary transducer, the slower flowing fluid at the outer edge of the tube would be exposed to an imaging beam for the longest amount of time, whereas the fluid at the center (with flow velocity  $V_{max}$  for parabolic flow) would be exposed to the beam for the least amount of time. In this case, if any artifact were observed, one would expect the most contrast to be destroyed on the outer edges, not in the center of the tube as our results indicate. This is not the case, however, for fluid exposed to a beam from a transducer moving along its axis of flow. In this case, once the translation speed exceeds the flow speed, the region exposed for the longest duration is the region where the flow speed is closest to the transducer motion speed, namely the region with the *fastest* flow, i.e. in the center of the tube. A theoretical calculation of contrast exposure time is shown in Figure 10. In Figure 11, the theoretical duration of exposure is shown along with a normalized intensity profile (inverted) measured from the image reconstructed in Figure 8.



**Figure 11.** Signal intensity across tube compared with ultrasound exposure time. The top graph represents a simplified prediction of the amount of time contrast agent would be exposed to the ultrasound beam for the conditions set in this particular experiment. The lower curve shows the normalized image intensity measured across the tube (far left image of Figure 8) as a function of radial distance from the center the tube averaged along the length of the tube (inverted for comparison: 1=black, 0=white). These measurements and calculations may help explain the central low scatter zone shown in the far right image of Figure 8.

## Key Research Accomplishments

- Conceptually modelled capillary refill in large and small vessels (Figure 1).
- Similarly modelled dual-transducer method for imaging capillary bed and deriving refill curves (Figure 2).
- Developed and tested electrical hardware and software for an early prototype of the imaging scan system.
- Built and tested initial temporary mobile stage for conducting dual transducer experiments.
- Designed and built permanent apparatus for transducer positioning and translation (Figure 3).
- Continued efforts in the development of electrical and controller interface for positioning system while software control is to likely be based on previous prototype.
- Demonstrated stability of contrast agent over time and demonstrated contrast destruction with transducer.
- Measured effect of contrast agent concentration on acquired signal intensity (Figure 4).
- For flash-echo pulse sequence, found linear relationship between contrast concentration and maximum projection image intensity (Figures 5-6), a newly hypothesized method of contrast agent imaging.
- Conducted dual transducer experiment on known laminar tube flow, and compared and contrasted results with single-transducer lateral case (Figures 7-8).
- Developed expression for contrast flow profile evolution with time and position, and compared with experimental results (Figure 9).
- Developed hypothesis that may explain contrast intensity variation across tube for moving transducer (Figures 10-11).

## Reportable Outcomes

The following were presented or submitted during the first year of the proposed research:

LeCarpentier GL, Chen NG, Fowlkes JB, and Carson PL: Preliminary results of a new method of 3D ultrasound contrast agent mapping of vascular anomalies for characterization of breast masses. Era of Hope, Department of Defense (DOD) Breast Cancer Research Program (BCRP), Orlando FL, September 25-28 2002, P29-6.

LeCarpentier GL, Chen NG, Fowlkes JB, and Carson PL: A new dual-transducer method of 3D ultrasound contrast agent imaging of vascularity. AIUM-hosted 10th Congress of the World Federation for Ultrasound in Medicine and Biology, 2003 (accepted).

## Conclusions

The preliminary results suggest that slow flow can be visualized and tracked at contrast agent concentrations relevant to clinical practice. In fact, the dual-transducer technique under current investigation may provide measures of tissue perfusion and refill characteristics which are unobtainable with current Doppler methods, although our recent analysis methods are well suited to contrast agent imaging quantification and breast mass characterization. Given the correlation of neo-vascularization and breast tumor growth, this imaging method has the potential of detecting anomalies and enhancing our understanding of changes in microvasculature at early stages of tumor development.

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## Appendix

The following abstract was submitted to and accepted by the AIUM-hosted 10th Congress of the World Federation for Ultrasound in Medicine and Biology:

### A New Dual-Transducer Method Of 3D Ultrasound Contrast Agent Imaging of Vascularity Gerald L LeCarpentier, Nelson G Chen NG, J Brian Fowlkes, and Paul L Carson

**Objective:** Although promising results have been achieved in assessing benign from malignant masses in the breast, prostate, and other organs using Doppler ultrasound (US), certain limitations remain. Of particular interest is slow flow and small vessel imaging in 3D. The purpose of this work is to develop a dual-transducer (DT) method of controlling the destruction and imaging of US contrast in 3D, aimed specifically at imaging vascular anomalies in these suspicious masses.

**Methods:** To date, all experimental procedures have been performed on flow phantoms. As controls, contrast (Definity) flows at various speeds and concentration were imaged laterally in a tube phantom using a GE Logic 9 in a contrast imaging mode (GE9). In the DT scenario, cross sectional images were acquired along the tube, and sequential scanning of image volumes acquired during contrast refill was performed. A Toshiba PowerVision 8000 (TPV) was used to destructively sweep the region and create a contrast-cleared front in the volume. The GE9 transducer followed behind that of the TPV and imaged continuously. The transducers were set various distances apart while both swept the region on a mounted and controlled motor system. The sweep speed was held constant such that the distances between the destruction and imaging transducers would correspond to particular times during refill. Sequential image volumes were reconstructed from the GE9 data sets.

**Results:** Contrast agent concentrations less than 4:10000 were linearly related to signal intensity in a 6 mm tube. In the control sets, the expected 2D parabolic evolution of the flow profile was seen. The DT images did not suffer the 2D limitation, and image planes reconstructed as slices along the tube displayed striking clarity and clear definition of flow profile information.

**Conclusions:** Preliminary results suggest that slow flow can be visualized and tracked in 3D, and the DT technique may provide measures of tissue refill characteristics unobtainable with current Doppler methods. Given the correlation of neo-vascularization and tumor growth, this imaging method has the potential of detecting and enhancing understanding of changes in microvasculature at early stages of tumor development.